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DESCRIPTION

THERAPEUTIC AGENT FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND METHOD FOR TREATING CHRONIC OBSTRUCTIVE PULMONARY DISEASE USING THE SAME

TECHNICAL FIELD

The present invention relates to a therapeutic agent for chronic obstructive pulmonary disease comprising, as an active ingredient, a 7-aminoquinolinone derivative and its physiologically acceptable salt, which is useful for treating chronic obstructive pulmonary disease, and a method for treating chronic obstructive pulmonary disease using the same.

BACKGROUND ART

With respect to a quinolinone derivative, general quinolinone derivatives such as 3-methoxy-4-hydroxy-1-methyl-2(1H)-quinolinone and 8-methoxy-3-methoxy-4-hydroxy-1-methyl-2(1H)-quinolinone have hitherto been known (see, for example, Non-Patent Document 1: "Journal of Heterocyclic Chemistry 22, pages 1087-1088, 1985 (J. Heterocyclic Chem., 22, 1985)"). However, such a document does not describe that these compounds are useful as a specific therapeutic agent.

Also there have been known quinolinone derivatives

which have oxygens directly bonded to carbons at the 3- and 4-positions and also have an amino group at the 7-position (see, for example, Patent Document 1: specification of U.S. Patent No. 5,942,521 and Patent Document 2: specification of U.S. Patent No. 6,136,822). In these documents, although an antiallergic action and an asthma treating action of a quinolinone derivative having an amino group have been studied, a therapeutic action against specific symptoms of chronic obstructive pulmonary disease through no antigen-antibody reaction has never been studied and also it has never been known that such a quinolinone derivative is effective as a therapeutic agent for chronic obstructive pulmonary disease.

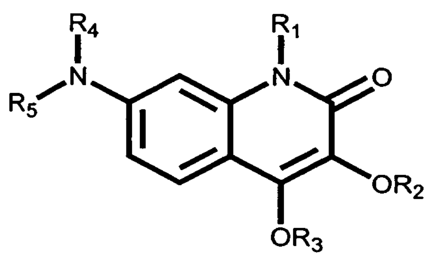
An object to be achieved by the present invention is to provide a therapeutic agent for chronic obstructive pulmonary disease, which has high safety and is effective on chronic obstructive pulmonary disease and also exhibits extremely excellent drug potency, and a method for treating chronic obstructive pulmonary disease using the same.

DISCLOSURE OF THE INVENTION

To achieve the above object, the present inventors have synthesized various compounds and evaluated drug potency and safety thereof. As a result, they have found that a specific aminoquinolinone derivative is extremely excellent as a

therapeutic agent for chronic obstructive pulmonary disease, and thus the present invention has been completed.

That is, the present invention is directed to a therapeutic agent for chronic obstructive pulmonary disease comprising, as an active ingredient, at least one of a 7-aminoquinolinone derivative represented by the general formula (I):



(I)

wherein R_1 represents a hydrogen atom or an alkyl group; R_2 and R_3 each represents a group selected from a hydrogen atom, an acyl group, an alkyl group and an alkenyl group; and R_4 and R_5 each represents a group selected from a hydrogen atom, an acyl group, an alkyl group, an alkenyl group and an aralkyl group, and its physiologically acceptable salt.

That is, the present invention is directed to use of at least one of the 7-aminoquinolinone derivative and its physiologically acceptable salt for treating chronic obstructive pulmonary disease.

Also, the present invention is directed to a therapeutic agent for chronic obstructive pulmonary disease comprising, as an active ingredient, the 7-aminoquinolinone derivative of the above general formula (1) and its

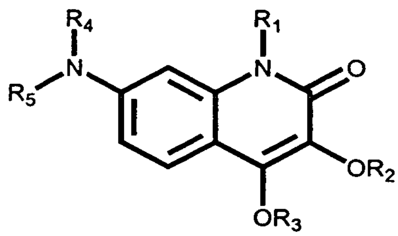
physiologically acceptable salt, wherein the chronic obstructive pulmonary disease is chronic bronchitis or pulmonary emphysema. That is, the present invention is directed to use of at least one of the 7-aminoquinolinone derivative and its physiologically acceptable salt for treating chronic bronchitis and pulmonary emphysema.

Furthermore, the present invention is directed to a method for treating chronic obstructive pulmonary disease, which comprises using the 7-aminoquinolinone derivative and its physiologically acceptable salt.

The present invention can provide a therapeutic agent for chronic obstructive pulmonary disease, which has high safety and also exhibits extremely excellent drug potency to chronic obstructive pulmonary disease, by using at least one of a specific 7-aminoquinolinone derivative and its physiologically acceptable salt as an active ingredient. That is, in the present invention, at least one of the 7-aminoquinolinone derivative and its physiologically acceptable salt is effective for treating chronic obstructive pulmonary disease.

BEST MODE FOR CARRYING OUT THE INVENTION

R_1 in the 7-aminoquinolinone derivative represented by the general formula (I):



(I)

of the present invention is a hydrogen atom or an alkyl group. The alkyl group in R_1 may be a linear or branched alkyl group.

Specific examples of the alkyl group include methyl group, ethyl group, propyl group, isopropyl group, n-butyl group, s-butyl group, n-pentyl group, hexyl group, octyl group and decyl group, and the alkyl group is preferably an alkyl group having 1 to 10 carbon atoms, and more preferably 1 to 8 carbon atoms.

R_2 and R_3 of the general formula (I) are a hydrogen atom, an acyl group, an alkyl group or an alkenyl group. Examples of the acyl group include alkanoyl group such as formyl group, acetyl group, propionyl group or butyryl group, and benzoyl group. The benzoyl group may have a substituent and examples thereof include p-hydroxybenzoyl group, p-methoxybenzoyl group, 2,4-dihydroxybenzoyl group and 2,4-dimethoxybenzoyl group. An alkanoyl group is preferable and an acetyl group is particularly preferable.

The alkyl group as for R_2 and R_3 may be a linear or branched alkyl group, and examples thereof include methyl group, ethyl group, propyl group, isopropyl group, n-butyl group, s-butyl group, n-pentyl group, hexyl group, octyl

group and decyl group, and the alkyl group is preferably an alkyl group having 1 to 10 carbon atoms, and more preferably an alkyl group having 1 to 8 carbon atoms.

The alkenyl group as for R_2 and R_3 may be a linear or branched alkenyl group, and examples thereof include vinyl group, propenyl group, hexenyl group, octenyl group, prenyl group and geranyl group, and the alkenyl group is preferably an alkenyl group having 2 to 10 carbon atoms.

In the general formula (I), R_4 and R_5 may be the same or different and represent a hydrogen atom, an acyl group, an alkyl group, an alkenyl group or an aralkyl group. Examples of the acyl group include alkanoyl group such as formyl group, acetyl group, propionyl group or butyryl group, benzoyl group, substituted benzoyl group, or cynnamoyl group which may be substituted.

Examples of the substituted benzoyl group include p-hydroxybenzoyl group, p-methoxybenzoyl group, 2,4-dihydroxybenzoyl group and 2,4-dimethoxybenzoyl group. Examples of the cinnamoyl group which may be substituted include cinnamoyl group, 2-hydroxycinnamoyl group, 3-hydroxycinnamoyl group, 4-hydroxycinnamoyl group, 3,4-dihydroxycinnamoyl group, 4-hydroxy-3-methoxycinnamoyl group, 3-hydroxy-4-methoxycinnamoyl group and 3,5-dimethoxy-4-hydroxycinnamoyl group. The cinnamoyl group is preferably cinnamoyl group which may be substituted.

The alkyl group as for R_4 and R_5 of the general formula (I) may be a linear or branched alkyl group, and examples thereof include methyl group, ethyl group, propyl group, isopropyl group, n-butyl group, s-butyl group, n-pentyl group, hexyl group, octyl group and decyl group. The alkyl group is preferably an alkyl group having 1 to 10 carbon atoms, and more preferably 1 to 8 carbon atoms.

The alkenyl group as for R_4 and R_5 may be a linear or branched alkenyl group, and examples thereof include vinyl group, propenyl group, hexenyl group, octenyl group, prenyl group and geranyl group. The alkenyl group is preferably an alkenyl group having 2 to 10 carbon atoms.

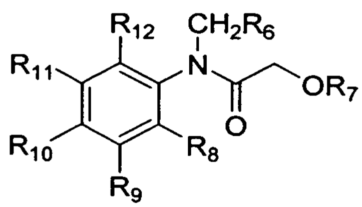
Examples of the aralkyl group as for R_4 and R_5 include aralkyl groups such as benzyl group and substituted benzyl group (for example, p-methoxybenzyl group or p-hydroxybenzyl group). The present invention also includes a 7-aminoquinolinone derivative in which substituents as for R_4 and R_5 of the 7-aminoquinolinone derivative represented by the general formula (I) are the same substituents, and a 7-aminoquinolinone derivative in which different substituents selected from the above group are combined.

The 7-aminoquinolinone derivative as the active ingredient of the therapeutic agent for chronic obstructive pulmonary disease of the present invention can be prepared by appropriately selecting a preferable method according to the

objective 7-aminoquinolinone derivative. For example, it can be prepared by the method described in Japanese Patent No. 2,943,725 or U.S. Patent No. 6,136,822.

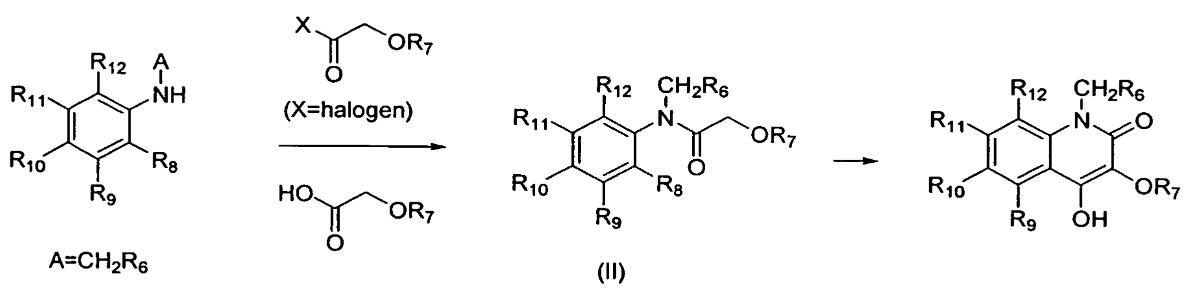
As an example, the method described in U.S. Patent No. 6,136,822 will now be described.

By reacting an amide derivative represented by the general formula (II):



(II)

with a basic substance, an intramolecular cyclization reaction is carried out as shown in the following scheme:



wherein R_6 represents a hydrogen atom, an alkyl group, an alkyl group having a hydroxyl group, an alkenyl group or an aryl group; R_7 represents an alkyl group, an alkenyl group, an aryl group or an aralkyl group; R_8 represents a reactive carboxyl group; R_9, R_{10} and R_{12} represent a hydrogen atom; and R_{11} represents $R_{13}R_{14}N$- (wherein R_{13} and R_{14} each independently represents a hydrogen atom, an alkyl group, an alkenyl group,

an aralkyl group or an acyl group).

Examples of the basic substance include various compounds such as alkali metal, alkali metal alkoxide, alkali earth metal alkoxide, alkali metal hydride, alkali earth metal hydride and alkali metal amide.

Examples of the alkali metal include alkali metals such as sodium and potassium, examples of the alkali metal alkoxide include basic substances such as sodium methoxide, sodium ethoxide, sodium t-butoxide and potassium t-butoxide, and examples of the alkali earth metal alkoxide include magnesium methoxide, magnesium ethoxide, magnesium t-butoxide , calcium methoxide, calcium ethoxide, calcium t-butoxide, barium methoxide, barium ethoxide and barium t-butoxide.

Examples of the alkali metal hydride include alkali metal hydrides such as lithium hydride, sodium hydride and potassium hydride, and examples of the alkali earth metal hydride include alkali earth metal hydrides such as calcium hydride. Examples of the alkali metal amide include lithium amide, sodium amide, potassium amide, lithium diisopropylamide, lithium bis(trimethylsilyl)amide and sodium bis(trimethylsilyl)amide and potassium bis(trimethylsilyl)amide.

The amount of the basic substance required for the cyclization reaction is usually from 1 to 5 mols, and

preferably from 2 to 3 mols, per mol of the amide derivative to be reacted. When sodium hydride, potassium t-butoxide or lithium diisopropylamide is used as the basic substance, enough amount is usually 2 mols per mol of the amide derivative.

The reaction in the method for preparing the 7-aminoquinolinone derivative is carried out in an organic solvent which does not inhibit the reaction. Examples of the organic solvent include hydrocarbon-based solvents such as benzene and toluene; alcohol-based solvents such as methanol, ethanol, propanol, isopropanol and t-butanol; ether-based solvents such as diethyl ether, tetrahydrofuran and 1,2-dimethoxyethane; and amide-based solvents such as N,N-dimethylformamide and 1-methyl-2-pyrolidinone.

Preferable organic solvent varies according to the kind of the basic substance to be used. For example, in case of the alkali metal alkoxide, an alcohol-based solvent is preferable. When the alkali metal amide such as lithium amide, sodium amide or potassium amide is used, ammonia can be used as the solvent.

The reaction temperature varies according to the kind of the basic substance and reaction solvent to be used, but is usually from -80°C to 100°C, and preferably from -50°C to 50°C, and the reaction time is usually from 1 to 5 hours.

Specific examples of the thus obtained 7-

aminoquinolinone derivative represented by the general formula (I) of the present invention include compounds represented by the following Tables 1 to 17.

Table 1

Compound No.	R_1	R_2	R_3	R_4	R_5
1	H	Acetyl	Methyl	H	H
2	H	Acetyl	Butyl	H	H
3	H	Acetyl	Hexyl	H	H
4	H	Acetyl	3-Methyl-2-butenyl	H	H
5	H	Acetyl	Geranyl	H	H
6	H	Acetyl	H	H	H
7	H	Formyl	Methyl	H	H
8	H	Formyl	Butyl	H	H
9	H	Formyl	Hexyl	H	H
10	H	Formyl	3-Methyl-2-butenyl	H	H
11	H	Formyl	Geranyl	H	H
12	H	Formyl	H	H	H
13	H	Methyl	Methyl	H	H
14	H	Methyl	Butyl	H	H
15	H	Methyl	Hexyl	H	H
16	H	Methyl	3-Methyl-2-butenyl	H	H
17	H	Methyl	Geranyl	H	H
18	H	Methyl	H	H	H
19	H	Isopropyl	H	H	H
20	H	Butyl	H	H	H
21	H	Hexyl	H	H	H
22	H	2-Methyl-pentyl	H	H	H
23	H	Octyl	H	H	H
24	H	2-Propenyl	H	H	H
25	H	Geranyl	H	H	H
26	H	H	H	H	H
27	H	H	Methyl	H	H
28	H	H	Butyl	H	H
29	H	H	Hexyl	H	H
30	H	H	3-Methyl-2-butenyl	H	H
31	H	H	Geranyl	H	H
32	Methyl	Acetyl	Methyl	H	H
33	Methyl	Acetyl	Ethyl	H	H
34	Methyl	Acetyl	Butyl	H	H
35	Methyl	Acetyl	Hexyl	H	H
36	Methyl	Acetyl	3-Methyl-2-butenyl	H	H
37	Methyl	Acetyl	Geranyl	H	H
38	Methyl	Acetyl	H	H	H
39	Methyl	Formyl	Methyl	H	H
40	Methyl	Formyl	Butyl	H	H

Table 2

Compound No.	R_1	R_2	R_3	R_4	R_5
41	Methyl	Formyl	Hexyl	H	H
42	Methyl	Formyl	3-Methyl-2-butenyl	H	H
43	Methyl	Formyl	Geranyl	H	H
44	Methyl	Formyl	H	H	H
45	Methyl	Methyl	Methyl	H	H
46	Methyl	Methyl	Butyl	H	H
47	Methyl	Methyl	Hexyl	H	H
48	Methyl	Methyl	3-Methyl-2-butenyl	H	H
49	Methyl	Methyl	Geranyl	H	H
50	Methyl	Methyl	H	H	H
51	Methyl	Isopropyl	H	H	H
52	Methyl	Butyl	H	H	H
53	Methyl	Hexyl	H	H	H
54	Methyl	2-Methyl-pentyl	H	H	H
55	Methyl	Octyl	H	H	H
56	Methyl	2-Propenyl	H	H	H
57	Methyl	Geranyl	H	H	H
58	Methyl	H	Methyl	H	H
59	Methyl	H	Butyl	H	H
60	Methyl	H	Hexyl	H	H
61	Methyl	H	3-Methyl-2-butenyl	H	H
62	Methyl	H	Geranyl	H	H
63	Methyl	H	H	H	H
64	Ethyl	Acetyl	Methyl	H	H
65	Ethyl	Acetyl	Ethyl	H	H
66	Ethyl	Acetyl	Butyl	H	H
67	Ethyl	Acetyl	Hexyl	H	H
68	Ethyl	Acetyl	3-Methyl-2-butenyl	H	H
69	Ethyl	Acetyl	Geranyl	H	H
70	Ethyl	Acetyl	H	H	H
71	Ethyl	Formyl	Methyl	H	H
72	Ethyl	Formyl	Butyl	H	H
73	Ethyl	Formyl	Hexyl	H	H
74	Ethyl	Formyl	3-Methyl-2-butenyl	H	H
75	Ethyl	Formyl	Geranyl	H	H
76	Ethyl	Formyl	H	H	H
77	Ethyl	Methyl	Methyl	H	H
78	Ethyl	Methyl	Butyl	H	H
79	Ethyl	Methyl	Hexyl	H	H
80	Ethyl	Methyl	3-Methyl-2-butenyl	H	H

Table 3

Compound No.	R_1	R_2	R_3	R_4	R_5
81	Ethyl	Methyl	Geranyl	H	H
82	Ethyl	Methyl	H	H	H
83	Ethyl	Isopropyl	H	H	H
84	Ethyl	Butyl	H	H	H
85	Ethyl	Hexyl	H	H	H
86	Ethyl	2-Methyl-pentyl	H	H	H
87	Ethyl	Octyl	H	H	H
88	Ethyl	2-Propenyl	H	H	H
89	Ethyl	Geranyl	H	H	H
90	Ethyl	H	Methyl	H	H
91	Ethyl	H	Butyl	H	H
92	Ethyl	H	Hexyl	H	H
93	Ethyl	H	3-Methyl-2-butenyl	H	H
94	Ethyl	H	Geranyl	H	H
95	Ethyl	H	H	H	H
96	Propyl	H	Methyl	H	H
97	Propyl	H	Propyl	H	H
98	Propyl	H	Butyl	H	H
99	Propyl	H	Decyl	H	H
100	Butyl	Acetyl	Methyl	H	H
101	Butyl	Acetyl	Ethyl	H	H
102	Butyl	Acetyl	Butyl	H	H
103	Butyl	Acetyl	Hexyl	H	H
104	Butyl	Acetyl	3-Methyl-2-butenyl	H	H
105	Butyl	Acetyl	Geranyl	H	H
106	Butyl	Acetyl	H	H	H
107	Butyl	Formyl	Methyl	H	H
108	Butyl	Formyl	Butyl	H	H
109	Butyl	Formyl	Hexyl	H	H
110	Butyl	Formyl	3-Methyl-2-butenyl	H	H
111	Butyl	Formyl	Geranyl	H	H
112	Butyl	Formyl	H	H	H
113	Butyl	Methyl	Methyl	H	H
114	Butyl	Methyl	Butyl	H	H
115	Butyl	Methyl	H	H	H
116	Butyl	Isopropyl	H	H	H
117	Butyl	Butyl	H	H	H
118	Butyl	Hexyl	H	H	H
119	Butyl	2-Methyl-pentyl	H	H	H
120	Butyl	Octyl	H	H	H

Table 4

Compound No.	R_1	R_2	R_3	R_4	R_5
121	Butyl	2-Propenyl	H	H	H
122	Butyl	Geranyl	H	H	H
123	Butyl	H	Methyl	H	H
124	Butyl	H	Butyl	H	H
125	Butyl	H	Hexyl	H	H
126	Butyl	H	3-Methyl-2-butenyl	H	H
127	Butyl	H	Geranyl	H	H
128	Butyl	H	H	H	H
129	Hexyl	Acetyl	Methyl	H	H
130	Hexyl	Acetyl	Ethyl	H	H
131	Hexyl	Acetyl	Butyl	H	H
132	Hexyl	Acetyl	Hexyl	H	H
133	Hexyl	Acetyl	3-Methyl-2-butenyl	H	H
134	Hexyl	Acetyl	Geranyl	H	H
135	Hexyl	Acetyl	H	H	H
136	Hexyl	Formyl	Methyl	H	H
137	Hexyl	Formyl	Butyl	H	H
138	Hexyl	Formyl	Hexyl	H	H
139	Hexyl	Formyl	3-Methyl-2-butenyl	H	H
140	Hexyl	Formyl	Geranyl	H	H
141	Hexyl	Formyl	H	H	H
142	Hexyl	Methyl	Methyl	H	H
143	Hexyl	Methyl	Butyl	H	H
144	Hexyl	Methyl	H	H	H
145	Hexyl	Isopropyl	H	H	H
146	Hexyl	Butyl	H	H	H
147	Hexyl	Hexyl	H	H	H
148	Hexyl	2-Methyl-pentyl	H	H	H
149	Hexyl	Octyl	H	H	H
150	Hexyl	2-Propenyl	H	H	H
151	Hexyl	Geranyl	H	H	H
152	Hexyl	H	Methyl	H	H
153	Hexyl	H	Butyl	H	H
154	Hexyl	H	Hexyl	H	H
155	Hexyl	H	3-Methyl-2-butenyl	H	H
156	Hexyl	H	Geranyl	H	H
157	Hexyl	H	H	H	H
158	Octyl	Acetyl	Methyl	H	H
159	Octyl	Acetyl	Ethyl	H	H
160	Octyl	Acetyl	Butyl	H	H

Table 5

Compound No.	R_1	R_2	R_3	R_4	R_5
161	Octyl	Acetyl	Hexyl	H	H
162	Octyl	Acetyl	3-Methyl-2-butenyl	H	H
163	Octyl	Acetyl	Geranyl	H	H
164	Octyl	Acetyl	H	H	H
165	Octyl	Formyl	Methyl	H	H
166	Octyl	Formyl	Butyl	H	H
167	Octyl	Formyl	Hexyl	H	H
168	Octyl	Formyl	3-Methyl-2-butenyl	H	H
169	Octyl	Formyl	Geranyl	H	H
170	Octyl	Formyl	H	H	H
171	Octyl	Methyl	Methyl	H	H
172	Octyl	Methyl	Butyl	H	H
173	Octyl	Methyl	H	H	H
174	Octyl	Isopropyl	H	H	H
175	Octyl	Butyl	H	H	H
176	Octyl	Hexyl	H	H	H
177	Octyl	2-Methyl-pentyl	H	H	H
178	Octyl	Octyl	H	H	H
179	Octyl	2-Propenyl	H	H	H
180	Octyl	Geranyl	H	H	H
181	Octyl	H	Methyl	H	H
182	Octyl	H	Butyl	H	H
183	Octyl	H	Hexyl	H	H
184	Octyl	H	3-Methyl-2-butenyl	H	H
185	Octyl	H	Geranyl	H	H
186	Octyl	H	H	H	H
187	H	Acetyl	Methyl	H	Hexyl
188	H	Acetyl	Butyl	H	Hexyl
189	H	Acetyl	Hexyl	H	Hexyl
190	H	Acetyl	3-Methyl-2-butenyl	H	Hexyl
191	H	Acetyl	Geranyl	H	Hexyl
192	H	Acetyl	H	H	Hexyl
193	H	Formyl	Methyl	H	Hexyl
194	H	Formyl	Butyl	H	Hexyl
195	H	Formyl	Hexyl	H	Hexyl
196	H	Formyl	3-Methyl-2-butenyl	H	Hexyl
197	H	Formyl	Geranyl	H	Hexyl
198	H	Formyl	H	H	Hexyl
199	H	Methyl	Methyl	H	Hexyl
200	H	Methyl	Butyl	H	Hexyl

Table 6

Compound No.	R_1	R_2	R_3	R_4	R_5
201	H	Methyl	Hexyl	H	Hexyl
202	H	Methyl	3-Methyl-2-butenyl	H	Hexyl
203	H	Methyl	Geranyl	H	Hexyl
204	H	Methyl	H	H	Hexyl
205	H	Isopropyl	H	H	Hexyl
206	H	Butyl	H	H	Hexyl
207	H	Hexyl	H	H	Hexyl
208	H	2-Methyl-pentyl	H	H	Hexyl
209	H	Octyl	H	H	Hexyl
210	H	2-Propenyl	H	H	Hexyl
211	H	Geranyloxy	H	H	Octyl
212	H	H	H	H	Octyl
213	H	H	Methyl	H	Octyl
214	H	H	Butyl	H	Octyl
215	H	H	Hexyl	H	Octyl
216	H	H	3-Methyl-2-butenyl	H	Octyl
217	H	H	Geranyl	H	Octyl
218	Methyl	Acetyl	Methyl	H	Ethyl
219	Methyl	Acetyl	Ethyl	H	Ethyl
220	Methyl	Acetyl	Butyl	H	Ethyl
221	Methyl	Acetyl	Hexyl	H	Ethyl
222	Methyl	Acetyl	3-Methyl-2-butenyl	H	Ethyl
223	Methyl	Acetyl	Geranyl	H	Ethyl
224	Methyl	Acetyl	H	H	Ethyl
225	Methyl	Formyl	Methyl	H	Ethyl
226	Methyl	Formyl	Butyl	H	Ethyl
227	Methyl	Formyl	Hexyl	H	Ethyl
228	Methyl	Formyl	3-Methyl-2-butenyl	H	Ethyl
229	Methyl	Formyl	Geranyl	H	Ethyl
230	Methyl	Formyl	H	H	Ethyl
231	Methyl	Methyl	Methyl	H	Ethyl
232	Methyl	Methyl	Butyl	H	Ethyl
233	Methyl	Methyl	Hexyl	H	Ethyl
234	Methyl	Methyl	3-Methyl-2-butenyl	H	Ethyl
235	Methyl	Methyl	Geranyl	H	Ethyl
236	Methyl	Methyl	H	H	Ethyl
237	Methyl	Isopropyl	H	H	Ethyl
238	Methyl	Butyl	H	H	Ethyl
239	Methyl	Hexyl	H	H	Ethyl
240	Methyl	2-Methyl-pentyl	H	H	Ethyl

Table 7

Compound No.	R_1	R_2	R_3	R_4	R_5
241	Methyl	Octyl	H	H	Ethyl
242	Methyl	2-Propenyl	H	H	Ethyl
243	Methyl	Geranyl	H	H	Ethyl
244	Methyl	H	Methyl	H	Ethyl
245	Methyl	H	Butyl	H	Ethyl
246	Methyl	H	Hexyl	H	Ethyl
247	Methyl	H	3-Methyl-2-butenyl	H	Ethyl
248	Methyl	H	Geranyl	H	Ethyl
249	Methyl	H	H	H	Ethyl
250	Ethyl	Acetyl	Methyl	H	Butyl
251	Ethyl	Acetyl	Ethyl	H	Butyl
252	Ethyl	Acetyl	Butyl	H	Butyl
253	Ethyl	Acetyl	Hexyl	H	Butyl
254	Ethyl	Acetyl	3-Methyl-2-butenyl	H	Butyl
255	Ethyl	Acetyl	Geranyl	H	Butyl
256	Ethyl	Acetyl	H	H	Butyl
257	Ethyl	Formyl	Methyl	H	Butyl
258	Ethyl	Formyl	Butyl	H	Butyl
259	Ethyl	Formyl	Hexyl	H	Butyl
260	Ethyl	Formyl	3-Methyl-2-butenyl	H	Butyl
261	Ethyl	Formyl	Geranyl	H	Butyl
262	Ethyl	Formyl	H	H	Butyl
263	Ethyl	Methyl	Methyl	H	Butyl
264	Ethyl	Methyl	Butyl	H	Butyl
265	Ethyl	Methyl	Hexyl	H	Butyl
266	Ethyl	Methyl	3-Methyl-2-butenyl	H	Butyl
267	Ethyl	Methyl	Geranyl	H	Butyl
268	Ethyl	Methyl	H	H	Butyl
269	Ethyl	Isopropyl	H	H	Butyl
270	Ethyl	Butyl	H	H	Butyl
271	Ethyl	Hexyl	H	H	Butyl
272	Ethyl	2-Methyl-pentyl	H	H	Butyl
273	Ethyl	Octyl	H	H	Butyl
274	Ethyl	2-Propenyl	H	H	Butyl
275	Ethyl	Geranyl	H	H	Butyl
276	Ethyl	H	Methyl	H	Butyl
277	Ethyl	H	Butyl	H	Butyl
278	Ethyl	H	Hexyl	H	Butyl
279	Ethyl	H	3-Methyl-2-butenyl	H	Butyl
280	Ethyl	H	Geranyl	H	Butyl

Table 8

Compound No.	R_1	R_2	R_3	R_4	R_5
281	Ethyl	H	H	H	Butyl
282	Propyl	H	Methyl	H	Butyl
283	Propyl	H	Propyl	H	Butyl
284	Propyl	H	Butyl	H	Butyl
285	Propyl	H	Decyl	H	Butyl
286	Butyl	Acetyl	Methyl	H	Methyl
287	Butyl	Acetyl	Ethyl	H	Methyl
288	Butyl	Acetyl	Butyl	H	Methyl
289	Butyl	Acetyl	Hexyl	H	Methyl
290	Butyl	Acetyl	3-Methyl-2-butenyl	H	Methyl
291	Butyl	Acetyl	Geranyl	H	Methyl
292	Butyl	Acetyl	H	H	Methyl
293	Butyl	Formyl	Methyl	H	Methyl
294	Butyl	Formyl	Butyl	H	Methyl
295	Butyl	Formyl	Hexyl	H	Methyl
296	Butyl	Formyl	3-Methyl-2-butenyl	H	Methyl
297	Butyl	Formyl	Geranyl	H	Methyl
298	Butyl	Formyl	H	H	Methyl
299	Butyl	Methyl	Methyl	H	Methyl
300	Butyl	Methyl	Butyl	H	Methyl
301	Butyl	Methyl	H	Methyl	Methyl
302	Butyl	Isopropyl	H	Methyl	Methyl
303	Butyl	Butyl	H	Methyl	Methyl
304	Butyl	Hexyl	H	Methyl	Methyl
305	Butyl	2-Methyl-pentyl	H	Methyl	Methyl
306	Butyl	Octyl	H	Methyl	Methyl
307	Butyl	2-Propenyl	H	Methyl	Methyl
308	Butyl	Geranyl	H	Methyl	Methyl
309	Butyl	H	Methyl	Methyl	Methyl
310	Butyl	H	Butyl	Methyl	Methyl
311	Butyl	H	Hexyl	Methyl	Methyl
312	Butyl	H	3-Methyl-2-butenyl	Methyl	Methyl
313	Butyl	H	Geranyl	Methyl	Methyl
314	Butyl	H	H	Methyl	Methyl
315	Hexyl	Acetyl	Methyl	H	Ethyl
316	Hexyl	Acetyl	Ethyl	H	Ethyl
317	Hexyl	Acetyl	Butyl	H	Ethyl
318	Hexyl	Acetyl	Hexyl	H	Ethyl
319	Hexyl	Acetyl	3-Methyl-2-butenyl	H	Ethyl
320	Hexyl	Acetyl	Geranyl	H	Ethyl

Table 9

Compound No.	R_1	R_2	R_3	R_4	R_5
321	Hexyl	Acetyl	H	H	Ethyl
322	Hexyl	Formyl	Methyl	H	Ethyl
323	Hexyl	Formyl	Butyl	H	Ethyl
324	Hexyl	Formyl	Hexyl	H	Ethyl
325	Hexyl	Formyl	3-Methyl-2-butenyl	H	Ethyl
326	Hexyl	Formyl	Geranyl	H	Ethyl
327	Hexyl	Formyl	H	H	Ethyl
328	Hexyl	Methyl	Methyl	H	Ethyl
329	Hexyl	Methyl	Butyl	H	Ethyl
330	Hexyl	Methyl	H	H	Ethyl
331	Hexyl	Isopropyl	H	H	Ethyl
332	Hexyl	Butyl	H	H	Ethyl
333	Hexyl	Hexyl	H	H	Ethyl
334	Hexyl	2-Methyl-pentyl	H	H	Ethyl
335	Hexyl	Octyl	H	H	Ethyl
336	Hexyl	2-Propenyl	H	H	Ethyl
337	Hexyl	Geranyl	H	H	Ethyl
338	Hexyl	H	Methyl	H	Ethyl
339	Hexyl	H	Butyl	H	Ethyl
340	Hexyl	H	Hexyl	H	Ethyl
341	Hexyl	H	3-Methyl-2-butenyl	H	Ethyl
342	Hexyl	H	Geranyl	H	Ethyl
343	Hexyl	H	H	H	Ethyl
344	Octyl	Acetyl	Methyl	H	Ethyl
345	Octyl	Acetyl	Ethyl	H	Ethyl
346	Octyl	Acetyl	Butyl	H	Ethyl
347	Octyl	Acetyl	Hexyl	H	Ethyl
348	Octyl	Acetyl	3-Methyl-2-butenyl	H	Ethyl
349	Octyl	Acetyl	Geranyl	H	Ethyl
350	Octyl	Acetyl	H	H	Ethyl
351	Octyl	Formyl	Methyl	H	Ethyl
352	Octyl	Formyl	Butyl	H	Ethyl
353	Octyl	Formyl	Hexyl	H	Ethyl
354	Octyl	Formyl	3-Methyl-2-butenyl	H	Ethyl
355	Octyl	Formyl	Geranyl	H	Ethyl
356	Octyl	Formyl	H	H	Ethyl
357	Octyl	Methyl	Methyl	H	Ethyl
358	Octyl	Methyl	Butyl	H	Ethyl
359	Octyl	Methyl	H	H	Ethyl
360	Octyl	Isopropyl	H	H	Ethyl

Table 10

Compound No.	R_1	R_2	R_3	R_4	R_5
361	Octyl	Butyl	H	H	Ethyl
362	Octyl	Hexyl	H	H	Ethyl
363	Octyl	2-Methyl-pentyl	H	H	Ethyl
364	Octyl	Octyl	H	H	Ethyl
365	Octyl	2-Propenyl	H	H	Ethyl
366	Octyl	Geranyl	H	H	Ethyl
367	Octyl	H	Methyl	H	Ethyl
368	Octyl	H	Butyl	H	Ethyl
369	Octyl	H	Hexyl	H	Ethyl
370	Octyl	H	3-Methyl-2-butenyl	H	Ethyl
371	Octyl	H	Geranyl	H	Ethyl
372	Octyl	H	H	H	Ethyl
373	Methyl	Acetyl	Methyl	Acetyl	Ethyl
374	Methyl	Acetyl	Ethyl	Acetyl	Ethyl
375	Methyl	Acetyl	Butyl	Acetyl	Ethyl
376	Methyl	Acetyl	Hexyl	Acetyl	Ethyl
377	Methyl	Acetyl	3-Methyl-2-butenyl	Acetyl	Ethyl
378	Methyl	Acetyl	Geranyl	Acetyl	Ethyl
379	Methyl	Acetyl	H	Acetyl	Ethyl
380	Methyl	Formyl	Methyl	Acetyl	Ethyl
381	Methyl	Formyl	Butyl	Acetyl	Ethyl
382	Methyl	Formyl	Hexyl	Acetyl	Ethyl
383	Methyl	Formyl	3-Methyl-2-butenyl	Acetyl	Ethyl
384	Methyl	Formyl	Geranyl	Acetyl	Ethyl
385	Methyl	Formyl	H	Acetyl	Ethyl
386	Methyl	Methyl	Methyl	H	Acetyl
387	Methyl	Methyl	Butyl	H	Acetyl
388	Methyl	Methyl	Hexyl	H	Acetyl
389	Methyl	Methyl	3-Methyl-2-butenyl	H	Acetyl
390	Methyl	Methyl	Geranyl	H	Acetyl
391	Methyl	Methyl	H	H	Acetyl
392	Methyl	Isopropyl	H	H	Acetyl
393	Methyl	Butyl	H	H	Acetyl
394	Methyl	Hexyl	H	H	Acetyl
395	Methyl	2-Methyl-pentyl	H	H	Acetyl
396	Methyl	Octyl	H	H	Acetyl
397	Methyl	2-Propenyl	H	H	Acetyl
398	Methyl	Geranyl	H	H	Acetyl
399	Methyl	H	Methyl	H	Acetyl
400	Methyl	H	Butyl	H	Acetyl

Table 11

Compound No.	R_1	R_2	R_3	R_4	R_5
401	Methyl	H	Hexyl	H	Acetyl
402	Methyl	H	3-Methyl-2-butenyl	H	Acetyl
403	Methyl	H	Geranyl	H	Acetyl
404	Methyl	H	H	H	Acetyl
405	Ethyl	Acetyl	Methyl	H	Acetyl
406	Ethyl	Acetyl	Ethyl	H	Acetyl
407	Ethyl	Acetyl	Butyl	H	Acetyl
408	Ethyl	Acetyl	Hexyl	H	Acetyl
409	Ethyl	Acetyl	3-Methyl-2-butenyl	H	Acetyl
410	Ethyl	Acetyl	Geranyl	H	Acetyl
411	Ethyl	Acetyl	H	H	Acetyl
412	Ethyl	Formyl	Methyl	H	Acetyl
413	Ethyl	Formyl	Butyl	H	Acetyl
414	Ethyl	Formyl	Hexyl	H	Acetyl
415	Ethyl	Formyl	3-Methyl-2-butenyl	H	Acetyl
416	Ethyl	Formyl	Geranyl	H	Acetyl
417	Ethyl	Formyl	H	H	Acetyl
418	Ethyl	Methyl	Methyl	H	Acetyl
419	Ethyl	Methyl	Butyl	H	Acetyl
420	Ethyl	Methyl	Hexyl	H	Acetyl
421	Ethyl	Methyl	3-Methyl-2-butenyl	H	Acetyl
422	Ethyl	Methyl	Geranyl	H	Acetyl
423	Ethyl	Methyl	H	H	Acetyl
424	Ethyl	Isopropyl	H	H	Acetyl
425	Ethyl	Butyl	H	H	Acetyl
426	Ethyl	Hexyl	H	H	Acetyl
427	Ethyl	2-Methyl-pentyl	H	H	Acetyl
428	Ethyl	Octyl	H	H	Acetyl
429	Ethyl	2-Propenyl	H	H	Acetyl
430	Ethyl	Geranyl	H	H	Acetyl
431	Ethyl	H	Methyl	H	Acetyl
432	Ethyl	H	Butyl	H	Acetyl
433	Ethyl	H	Hexyl	H	Acetyl
434	Ethyl	H	3-Methyl-2-butenyl	H	Acetyl
435	Ethyl	H	Geranyl	H	Acetyl
436	Ethyl	H	H	H	Acetyl
437	Propyl	H	Methyl	H	Acetyl
438	Propyl	H	Propyl	H	Acetyl
439	Propyl	H	Butyl	H	Acetyl
440	Propyl	H	Decyl	H	Acetyl

Table 12

Compound No.	R_1	R_2	R_3	R_4	R_5
441	Butyl	Acetyl	Methyl	H	Formyl
442	Butyl	Acetyl	Ethyl	H	Formyl
443	Butyl	Acetyl	Butyl	H	Formyl
444	Butyl	Acetyl	Hexyl	H	Formyl
445	Butyl	Acetyl	3-Methyl-2-butenyl	H	Formyl
446	Butyl	Acetyl	Geranyl	H	Formyl
447	Butyl	Acetyl	H	H	Formyl
448	Butyl	Formyl	Methyl	H	Formyl
449	Butyl	Formyl	Butyl	H	Formyl
450	Butyl	Formyl	Hexyl	H	Formyl
451	Butyl	Formyl	3-Methyl-2-butenyl	H	Formyl
452	Butyl	Formyl	Geranyl	H	Formyl
453	Butyl	Formyl	H	H	Formyl
454	Butyl	Methyl	Methyl	H	Formyl
455	Butyl	Methyl	Butyl	H	Formyl
456	Butyl	Methyl	H	H	Formyl
457	Butyl	Isopropyl	H	H	Formyl
458	Butyl	Butyl	H	H	Formyl
459	Butyl	Hexyl	H	H	Formyl
460	Butyl	2-Methyl-pentyl	H	H	Formyl
461	Butyl	Octyl	H	H	Formyl
462	Butyl	2-Propenyl	H	H	Formyl
463	Butyl	Geranyl	H	H	Formyl
464	Butyl	H	Methyl	H	Formyl
465	Butyl	H	Butyl	H	Formyl
466	Butyl	H	Hexyl	H	Formyl
467	Butyl	H	3-Methyl-2-butenyl	H	Formyl
468	Butyl	H	Geranyl	H	Formyl
469	Butyl	H	H	H	Formyl
470	Hexyl	Acetyl	Methyl	H	Propionyl
471	Hexyl	Acetyl	Ethyl	H	Propionyl
472	Hexyl	Acetyl	Butyl	H	Propionyl
473	Hexyl	Acetyl	Hexyl	H	Propionyl
474	Hexyl	Acetyl	3-Methyl-2-butenyl	H	Propionyl
475	Hexyl	Acetyl	Geranyl	H	Propionyl
476	Hexyl	Acetyl	H	H	Propionyl
477	Hexyl	Formyl	Methyl	H	Propionyl
478	Hexyl	Formyl	Butyl	H	Propionyl
479	Hexyl	Formyl	Hexyl	H	Propionyl
480	Hexyl	Formyl	3-Methyl-2-butenyl	H	Propionyl

Table 13

Compound No.	R_1	R_2	R_3	R_4	R_5
481	Hexyl	Formyl	Geranyl	H	Propionyl
482	Hexyl	Formyl	H	H	Propionyl
483	Hexyl	Methyl	Methyl	H	Propionyl
484	Hexyl	Methyl	Butyl	H	Propionyl
485	Hexyl	Methyl	H	H	Propionyl
486	Hexyl	Isopropyl	H	H	Propionyl
487	Hexyl	Butyl	H	H	Propionyl
488	Hexyl	Hexyl	H	H	Propionyl
489	Hexyl	2-Methyl-pentyl	H	H	Propionyl
490	Hexyl	Octyl	H	H	Propionyl
491	Hexyl	2-Propenyl	H	H	Propionyl
492	Hexyl	Geranyl	H	H	Propionyl
493	Hexyl	H	Methyl	H	Propionyl
494	Hexyl	H	Butyl	H	Propionyl
495	Hexyl	H	Hexyl	H	Propionyl
496	Hexyl	H	3-Methyl-2-butenyl	H	Propionyl
497	Hexyl	H	Geranyl	H	Propionyl
498	Hexyl	H	H	H	Propionyl
499	Octyl	Acetyl	Methyl	H	Propionyl
500	Octyl	Acetyl	Ethyl	H	Benzoyl
501	Octyl	Acetyl	Butyl	H	Benzoyl
502	Octyl	Acetyl	Hexyl	H	Benzoyl
503	Octyl	Acetyl	3-Methyl-2-butenyl	H	Benzoyl
504	Octyl	Acetyl	Geranyl	H	Benzoyl
505	Octyl	Acetyl	H	H	Benzoyl
506	Octyl	Formyl	Methyl	H	Benzoyl
507	Octyl	Formyl	Butyl	H	Benzoyl
508	Octyl	Formyl	Hexyl	H	Benzoyl
509	Octyl	Formyl	3-Methyl-2-butenyl	H	Benzoyl
510	Octyl	Formyl	Geranyl	H	Benzoyl
511	Octyl	Formyl	H	H	Benzoyl
512	Octyl	Methyl	Methyl	H	Benzoyl
513	Octyl	Methyl	Butyl	H	Benzoyl
514	Methyl	Methyl	H	H	Benzoyl
515	Methyl	Isopropyl	H	H	Benzoyl
516	Methyl	Butyl	H	H	Benzoyl
517	Methyl	Hexyl	H	H	Benzoyl
518	Methyl	2-Methyl-pentyl	H	H	Benzoyl
519	Methyl	Octyl	H	H	Benzoyl
520	Methyl	2-Propenyl	H	H	Benzoyl

Table 14

Compound No.	R_1	R_2	R_3	R_4	R_5
521	Methyl	Geranyl	H	H	Benzoyl
522	Butyl	H	Methyl	H	Benzoyl
523	Butyl	H	Butyl	H	Benzoyl
524	Butyl	H	Hexyl	H	Benzoyl
525	Butyl	H	3-Methyl-2-butenyl	H	Benzoyl
526	Butyl	H	Geranyl	H	Benzoyl
527	Butyl	H	H	H	Benzoyl
528	Methyl	Acetyl	Methyl	H	Cinnamoyl
529	Methyl	Acetyl	Ethyl	H	Cinnamoyl
530	Methyl	Acetyl	Butyl	H	Cinnamoyl
531	Methyl	Acetyl	Hexyl	H	Cinnamoyl
532	Methyl	Acetyl	3-Methyl-2-butenyl	H	Cinnamoyl
533	Methyl	Acetyl	Geranyl	H	Cinnamoyl
534	Methyl	Acetyl	H	H	Cinnamoyl
535	Methyl	H	Methyl	H	Cinnamoyl
536	Methyl	H	Butyl	H	Cinnamoyl
537	Methyl	H	Hexyl	H	Cinnamoyl
538	Methyl	H	3-Methyl-2-butenyl	H	Cinnamoyl
539	Methyl	H	Geranyl	H	Cinnamoyl
540	Methyl	H	H	H	Cinnamoyl
541	Methyl	Methyl	Methyl	H	3,5-Dimethoxy-4-hydroxycinnamoyl
542	Methyl	Methyl	Butyl	H	3,5-Dimethoxy-4-hydroxycinnamoyl
543	Methyl	Methyl	Hexyl	H	3,5-Dimethoxy-4-hydroxycinnamoyl
544	Methyl	Methyl	3-Methyl-2-butenyl	H	3,5-Dimethoxy-4-hydroxycinnamoyl
545	Methyl	Methyl	Geranyl	H	3,5-Dimethoxy-4-hydroxycinnamoyl
546	Methyl	Methyl	H	H	3,5-Dimethoxy-4-hydroxycinnamoyl
547	Methyl	Isopropyl	H	H	3,5-Dimethoxy-4-hydroxycinnamoyl
548	Methyl	Butyl	H	H	3,5-Dimethoxy-4-hydroxycinnamoyl
549	Methyl	Hexyl	H	H	3,5-Dimethoxy-4-hydroxycinnamoyl
550	Methyl	2-Methyl-pentyl	H	H	3,5-Dimethoxy-4-hydroxycinnamoyl

Table 15

Compound No.	R_1	R_2	R_3	R_4	R_5
551	Methyl	Octyl	H	H	3,5-Dimethoxy-4-hydroxycinnamoyl
552	Methyl	2-Propenyl	H	H	3,5-Dimethoxy-4-hydroxycinnamoyl
553	Methyl	Geranyl	H	H	3,5-Dimethoxy-4-hydroxycinnamoyl
554	Methyl	H	Methyl	H	3,5-Dimethoxy-4-hydroxycinnamoyl
555	Methyl	H	Butyl	H	3,5-Dimethoxy-4-hydroxycinnamoyl
556	Methyl	H	Hexyl	H	3,5-Dimethoxy-4-hydroxycinnamoyl
557	Methyl	H	3-Methyl-2-butenyl	H	3,5-Dimethoxy-4-hydroxycinnamoyl
558	Methyl	H	Geranyl	H	3,5-Dimethoxy-4-hydroxycinnamoyl
559	Methyl	H	H	H	3,5-Dimethoxy-4-hydroxycinnamoyl
560	Ethyl	Acetyl	Methyl	H	4-Hydroxy-3-methoxycinnamoyl
561	Ethyl	Acetyl	Ethyl	H	4-Hydroxy-3-methoxycinnamoyl
562	Ethyl	Acetyl	Butyl	H	4-Hydroxy-3-methoxycinnamoyl
563	Ethyl	Acetyl	Hexyl	H	4-Hydroxy-3-methoxycinnamoyl
564	Ethyl	Acetyl	3-Methyl-2-butenyl	H	4-Hydroxy-3-methoxycinnamoyl
565	Ethyl	Acetyl	Geranyl	H	4-Hydroxy-3-methoxycinnamoyl
566	Ethyl	Acetyl	H	H	4-Hydroxy-3-methoxycinnamoyl
567	Ethyl	Formyl	Methyl	H	4-Hydroxy-3-methoxycinnamoyl
568	Ethyl	Formyl	Butyl	H	4-Hydroxy-3-methoxycinnamoyl
569	Ethyl	Formyl	Hexyl	H	4-Hydroxy-3-methoxycinnamoyl
570	Ethyl	Formyl	3-Methyl-2-butenyl	H	4-Hydroxy-3-methoxycinnamoyl

Table 16

Compound No.	R_1	R_2	R_3	R_4	R_5
571	Ethyl	Formyl	Geranyl	H	4-Hydroxy-3-methoxycinnamoyl
572	Ethyl	Formyl	H	H	4-Hydroxy-3-methoxycinnamoyl
573	Methyl	Methyl	Methyl	H	4-Hydroxy-3-methoxycinnamoyl
574	Methyl	Methyl	Butyl	H	4-Hydroxy-3-methoxycinnamoyl
575	Methyl	Methyl	Hexyl	H	4-Hydroxy-3-methoxycinnamoyl
576	Methyl	Methyl	3-Methyl-2-butenyl	H	4-Hydroxy-3-methoxycinnamoyl
577	Methyl	Methyl	Geranyl	H	4-Hydroxy-3-methoxycinnamoyl
578	Methyl	Methyl	H	H	4-Hydroxy-3-methoxycinnamoyl
579	Methyl	Isopropyl	H	H	4-Hydroxy-3-methoxycinnamoyl
580	Methyl	Butyl	H	H	4-Hydroxy-3-methoxycinnamoyl
581	Methyl	Hexyl	H	H	4-Hydroxy-3-methoxycinnamoyl
582	Methyl	2-Methyl-pentyl	H	H	4-Hydroxy-3-methoxycinnamoyl
583	Methyl	Octyl	H	H	4-Hydroxy-3-methoxycinnamoyl
584	Methyl	2-Propenyl	H	H	4-Hydroxy-3-methoxycinnamoyl
585	Methyl	Geranyl	H	H	4-Hydroxy-3-methoxycinnamoyl
586	Methyl	H	Methyl	H	Benzyl
587	Methyl	H	Butyl	H	Benzyl
588	Methyl	H	Hexyl	H	Benzyl
589	Methyl	H	3-Methyl-2-butenyl	H	Benzyl
590	Methyl	H	Geranyl	H	Benzyl
591	Methyl	H	H	H	Benzyl
592	Propyl	H	Methyl	H	Benzyl
593	Propyl	H	Propyl	H	Benzyl
594	Propyl	H	Butyl	H	Benzyl
595	Propyl	H	Decyl	H	Benzyl

Table 17

Compound No.	R_1	R_2	R_3	R_4	R_5
596	Methyl	Methyl	H	H	2-Propenyl
597	Methyl	Isopropyl	H	H	2-Propenyl
598	Methyl	Butyl	H	H	2-Propenyl
599	Methyl	Hexyl	H	H	2-Propenyl
600	Methyl	2-Methyl-pentyl	H	H	2-Propenyl
601	Methyl	Octyl	H	H	2-Propenyl
602	Methyl	2-Propenyl	H	H	2-Propenyl
603	Methyl	Geranyl	H	H	2-Propenyl
604	Methyl	H	Methyl	H	2-Propenyl
605	Methyl	H	Butyl	H	2-Propenyl
606	Methyl	H	Hexyl	H	2-Propenyl
607	Methyl	H	3-Methyl-2-butenyl	H	2-Propenyl
608	Methyl	H	Geranyl	H	2-Propenyl
609	Methyl	H	H	H	2-Propenyl
610	Methyl	H	Methyl	H	2-Propenyl
611	Methyl	H	Propyl	H	2-Propenyl
612	Methyl	H	Butyl	H	2-Propenyl
613	Methyl	H	Decyl	H	2-Propenyl
614	Methyl	Methyl	H	H	Geranyl
615	Methyl	Isopropyl	H	H	Geranyl
616	Methyl	Butyl	H	H	Geranyl
617	Methyl	Hexyl	H	H	Geranyl
618	Methyl	2-Methyl-pentyl	H	H	Geranyl
619	Methyl	Octyl	H	H	Geranyl
620	Methyl	2-Propenyl	H	H	Geranyl
621	Methyl	Geranyl	H	H	Geranyl
622	Methyl	H	Methyl	H	Geranyl
623	Methyl	H	Butyl	H	Geranyl
624	Methyl	H	Hexyl	H	Geranyl
625	Methyl	H	3-Methyl-2-butenyl	H	Geranyl
626	Methyl	H	Geranyl	H	Geranyl
627	Methyl	H	H	H	Geranyl
628	Methyl	H	Methyl	H	Geranyl
629	Methyl	H	Propyl	H	Geranyl
630	Methyl	H	Butyl	H	Geranyl

In the present invention, physiologically acceptable salts of these compounds are also included. As used herein, physiologically acceptable salts refer to alkali addition salts having no toxicity with respect to compounds having a hydroxyl group, especially compounds having a hydroxyl group at the 3- and/or 4-positions among the above-described compounds, and examples thereof include nontoxic salts such as sodium salt, potassium salt, magnesium salt, calcium salt, ammonium salt and nontoxic amine salt. These salts can be prepared by a conventionally known method.

With respect to the compound having no hydroxyl group, there can be exemplified nontoxic addition salts prepared by reacting an amino group of an aromatic ring with mineral acids such as hydrochloric acid, sulfuric acid and phosphoric acid, or various organic acids such as acetic acid, propionic acid, succinic acid, tartaric acid, maleic acid and fumaric acid, or sulfonic acids such as methanesulfonic acid. These salts can be prepared by a conventionally known method.

As described in the examples described hereinafter, the 7-aminoquinolinone derivative and its physiologically acceptable salt thereof in the present invention have low toxicity and are extremely useful as a therapeutic agent for chronic obstructive pulmonary disease for treating or preventing various chronic obstructive pulmonary diseases.

Chronic obstructive pulmonary disease as used herein

refers to lung diseases including chronic bronchitis and pulmonary emphysema. Chronic obstructive pulmonary disease is generally characterized by progressive and irreversible airflow limitation. In many cases, it is accompanied by airway hyper-responsiveness and some chronic obstructive pulmonary disease is reversible symptom. Chronic bronchitis is characterized by chronic moist cough for 3 or more consecutive months in each of consecutive 2 years. Pulmonary emphysema is an permanent abnormal swelling of alveoli distal to terminal bronchiole, which is accompanied by destructive changes of pulmonary alveolus walls and having no obvious fibrosis. Destructive change is defined as irregular swelling of respiratory air spaces, wherein regular appearances of pulmonary acinuses and its components may be destroyed and disappeared.

As described above, chronic obstructive pulmonary disease is characterized by irreversible airflow limitation and has a pathologic characteristic different from asthma, which is a reversible airflow limitation. Furthermore, in international asthma therapy guideline, "Guideline for the Diagnosis and Management of Asthma (NHLBI, 2002)", inhalation steroids for drug treatment against bronchial asthma are recommended as a first choice and its excellent effectiveness is confirmed. However, in the similar global guideline, Global initiative for chronic obstructive lung disease (GOLD;

NHLBI/WHO, 1998), the effect of steroids on chronic obstructive pulmonary disease is a little and therefore its use is not recommended well. Thus, chronic obstructive pulmonary disease and bronchial asthma have different responses to drugs.

Main therapy for chronic obstructive pulmonary disease is use of bronchodilator such as anticholinergic agents and β-receptor agonists, wherein a symptomatic therapy for relaxing temporarily airway obstructive state is carried out. Recently, research and development of a long-acting anticholinergic agent and β receptor agonist has been carried out, but any of them belongs to a symptomatic therapy. The risk factor of chronic obstructive pulmonary disease is noxious micro particles due to smoking and air pollution. It is believed that lasting chronic inflammation state in peripheral respiratory tract and pulmonary alveoli due to long-term exposure of them is the cause for the disease development. That is, the above mentioned GOLD describes clearly that there is observed neutrophilic inflammation in a lung and that important one as its causal and progressive factor is inflammation due to imbalance between a protease and a protease inhibitor, and oxidative stress. However, any agents capable of treating chronic obstructive pulmonary disease by suppressing such inflammation have never been marketed.

The present inventors have paid attention to airway inflammation due to oxidative stress, which is considered to as an important factor for the onset of chronic obstructive pulmonary disease, made an animal model corresponding to chronic obstructive pulmonary disease and intensively studied about a drug capable of treating airway inflammation in the model. Consequently, they have found a compound which exerts a potent therapeutic effect in a model in which the airway is exposed to peroxynitrite, a potent oxidant produced in the body described in GOLD, to induce airway hyper-responsiveness.

It is suggested that chronic obstructive pulmonary disease is also involved in air pollution substances and it is known that, when exposing animals such as rat and guinea pig to ozone, one of air pollution substances, airway inflammation, including airway hyper-responsiveness, similar to chronic obstructive pulmonary disease is induced. Therefore, the present inventors have investigated effectiveness of the compounds of the present invention against a test model in which airway hyper-responsiveness is induced by exposure of ozone to guinea pig, and thus obtaining such a finding that the compounds of the present invention have equal or greater effectiveness than that of the conventional agents and are therefore extremely useful as a agent for chronic obstructive pulmonary disease.

The therapeutic agent for chronic obstructive pulmonary

disease of the present invention can be administered orally (taken internally or inhaled) or parenterally (e.g., intravenous administration, subcutaneous administration, transcutaneous administration or intrarectal administration), and can be prepared into a formulation form suitable for the respective administration method at the time of administration.

The formulation can be prepared in various formulation forms such as tablets, capsules, granules, grains, powders, troches, sublingual formulations, suppositories, ointments, injections, emulsions, suspensions and syrups according to the specific application.

When preparing these formulations, said formulations can be formulated in accordance with known methods using non-toxic additives normally used in this type of formulation, examples of which include vehicles, binders, disintegration agents, lubricants, preservatives, antioxidants, isotonic agents, buffers, coating agents, correctives, dissolving assistants, bases, dispersants, stabilizers and colorants. Specific examples of these nontoxic additives are listed below.

Examples of vehicles include starch and its derivatives (such as dextrin and carboxymethyl starch), cellulose and its derivatives (such as methyl cellulose and hydroxypropyl cellulose), saccharides (such as lactose, refined sugar and

glucose), silicic acid and silicates (such as naturally-occurring aluminum silicate and magnesium silicate), carbonates (such as calcium carbonate, magnesium carbonate, and sodium hydrogen carbonate), aluminum-magnesium hydroxide, synthetic hydrotalcite, polyoxythylene derivatives, glycerin monostearate and sorbitan monooleate.

Examples of binders include starch and its derivatives (such as pregelatinized starch and dextrin), cellulose and its derivatives (such as ethyl cellulose, sodium carboxymethyl cellulose and hydroxypropylmethyl cellulose), gum arabic, tragacanth gum, gelatin, saccharides (such as glucose and refined sugar), ethanol and polyvinyl alcohol.

Examples of disintegration agents include starch and its derivatives (such as carboxymethyl starch and hydroxypropyl starch), cellulose and its derivatives (such as sodium carboxymethyl cellulose, crystal cellulose and hydroxypropylmethyl cellulose), carbonates (such as calcium carbonate and calcium hydrogen carbonate), tragacanth gum, gelatin and agar.

Examples of lubricants include stearic acid, calcium stearate, magnesium stearate, talc, silicic acid and its salts (such as light silicic anhydride and naturally-occurring aluminum silicate), titanium oxide, calcium hydrogen phosphate, dry aluminum hydroxide gel and macrogall.

Examples of preservatives include paraoxybenzoate

esters, sulfites (such as sodium sulfite and sodium pyrosulfite), phosphates (such as sodium phosphate, calcium polyphosphate, sodium polyphosphate and sodium metaphosphate), alcohols (such as chlorobutanol and benzyl alcohol), benzalkonium chloride, benzetonium chloride, phenol, cresol, chlorocresol, dehydroacetic acid, sodium dehydroacetate, glycerin sorbate and saccharides.

Examples of antioxidants include sulfites (such as sodium sulfite and sodium hydrogen sulfite), rongalite, erysorbic acid, L-ascorbic acid, cysteine thioglycerol, butylhydroxy anisole, dibutylhydroxy toluene, propyl gallate, ascorbic palmitate and dl-α-tocopherol.

Examples of isotonic agents include sodium chloride, sodium nitrate, potassium nitrate, dextrin, glycerin and glucose. In addition, examples of buffers include sodium carbonate, hydrochloric acid, boric acid and phosphates (such as sodium hydrogen phosphate).

Examples of coating agents include cellulose derivatives (such as hydroxypropyl cellulose, cellulose acetophthalate and hydroxypropyl methyl cellulose phthalate), shellac, polyvinyl pyrrolidone, polyvinyl pyridines (such as poly-2-vinylpyridine and poly-2-vinyl-5-ethylpyridine), polyvinylacetyldiethylaminoacetate, polyvinyl alcohol phthalate and methacrylate-methacrylic acid copolymer.

Examples of correctives include saccharides (such as

glucose, refined sugar and lactose), sodium saccharine and sugar-alcohols. Examples of dissolving assistants include ethylenediamine, nicotinic amide, sodium saccharine, citric acid, citrates, sodium benzoate, soaps, polyvinyl pyrrolidone, polysorbates, sorbitan fatty acid esters, glycerin, polypropylene glycol and benzyl alcohol.

Examples of bases include fats (such as lard), vegetable oils (such as olive oil and sesame oil), animal oils, lanolinic acid, vaseline, paraffin, wax, resin, bentonite, glycerin, glycolic oil and higher alcohols (such as stearyl alcohol and cetanol).

Examples of dispersants include gum arabic, tragacanth gum, cellulose derivatives (such as methyl cellulose), stearate polyesters, sorbitan sesquioleates, aluminum monostearate, sodium alginate, polysorbates and sorbitan fatty acid esters. In addition, examples of stabilizers include sulfites (such as sodium bisulfite), nitrogen and carbon dioxide.

In addition, although the content of the 7-aminoquinolinone derivative and its physiologically acceptable salt thereof in this formulation varies according to the formulation form. In general, it is preferably contained at the concentration of 0.01 to 100% by weight.

Although the dose of the therapeutic agent for chronic obstructive pulmonary disease of the present invention can be

varied over a wide range according to the target species of warm-blooded animal including humans, the severity of the symptoms and the diagnosis of a physician. In general, in the case of oral administration, the dose as the amount of active ingredient is from 0.01 to 50 mg, and preferably from 0.05 to 10 mg, per day per 1 kg of body weight.

In the case of parenteral administration, the dose as the amount of active ingredient is from 0.01 to 10 mg, and preferably from 0.01 to 5 mg, per day per 1 kg of body weight. In addition, the above dose can be administered in a single administration or divided into several administrations, and can be suitably varied according to the severity of patient symptoms and diagnosis of a physician.

EXAMPLES

The following examples are intended to illustrate the present invention, but the scope of the present invention is not limited by the following examples.

(Example 1) Acute toxicity test in mice

This test was performed so as to investigate safety of the quinolinone derivatives of the present invention. The test procedure will now be described.

(Test procedure)

Each of 7-aminoquinolinone derivatives (compounds 32, 53, 55, 56, 58, 87, 147, 173, 181, 204, 236, 276, 303, 309,

330, 359, 396, 401, 459, 514, 519, 546 to 556, and 581) was forcibly administered orally at the doses of 1000 and 2000 mg/kg to male ICR mice (body weight is 20 to 25 g, 5 mice per one group), using feeding tubes for mice.

After the administration, the animals were kept in cages for 7 days. Then, general symptoms were observed and the number of dead animals was counted. 50% lethal dose (LD_{50}: mg/kg) was extrapolated from the mortality at 7th day after administration. As a result, the LD_{50} of all aminoquinolinone derivatives was 1000 mg/kg or more, and therefore it was clearly demonstrated that the aminoquinolinone derivatives of the present invention have extremely high safety.

(Example 2)

This test was performed so as to investigate the pharmacological effect of the 7-aminoquinolinone derivative of the present invention on an airway hyper-responsiveness model induced by exposure of peroxynitrite in guinea pigs. The test procedure will now be described.

(Preparation of airway hyper-responsiveness model)

Guinea pigs were fasted for 18 hours or more. The animals were administrated the test substance (30 mg/kg) orally one hour before exposure of peroxynitrite and the neck was dissected under ether anesthesia, and then the trachea was exposed. 0.1 mL of 1 mmol/L peroxynitrite was

administered intratracheally into pulmonary side by pushing with air and, after the administration, the incision was sutured and disinfected.

(Measurement of airway hyper-responsiveness to histamine)

The measurement of airway hyper-responsiveness was performed on 5-day, taking the day of model preparation 0-day. Guinea pigs were fasted for 18 hours or more. The measurement of lung resistance; (RLung) was performed according to the method of R. E. Giles et al. (R. E. Giles, M. P. Finkel and J. Mazurowski: Use of an Analog On-Line Computer for the Evaluation of Pulmonary Resistance and Dynamic Compliance in the Anesthetized Dog. Arch. Int. Pharmacodyn. 194, 213-222 (1971)). That is, the animals were anesthetized with Nembutal (Trade name: 40 mg/kg, i.v., sodium pentobarbital) and subjected to cannulation into esophagus, trachea and jugular veins (for administration of histamine). The esophagus and trachea cannulas were connected to an artificial respirator (ventilation volume: 6 mL/kg, ventilation frequency: 60 times/min, SN-480-7) and the Rlung was measured after intravenous administration (dose of 0.1 mL/kg) of physiological saline solution and histamine (32 μg/kg) using a total plethysmograph system via flow sensor, connected to Validyne DF45F (for flow rate) and DP45P (for pressure). RLung before administration was determined by averaging values of any 3 out of 20 breaths, RLung after

administration of physiological saline solution was determined by averaging values of any 3 out of 5 breaths, and RLung after administration of histamine was determined by averaging values of the following 3 breaths; 1) showing the maximum lung resistance, 2) taken just before and 3) taken just after the one with the maximum lung resistance, out less than 20 breaths. (The extreme values in RLung that occurred when animal moved during the measurement were excluded from the calculations.)

The percentage of increase in lung resistance was calculated by the following equation.

Increase in lung resistance (%) = ([RLung after administration of histamine] - [RLung before administration]) / [RLung before administration] × 100

Table 18

Increase in lung resistance (%)

Compound	Increase (%)	Compound	Increase (%)
32	435	359	431
53	440	396	421
55	425	401	420
56	434	459	427
58	423	514	434
87	432	519	440
147	429	546	422
173	430	549	423
181	425	551	416
204	439	553	417
236	428	556	426
276	430	581	430

303	427	Control group	759
309	435	Non-stimulation group	382
330	417		

From the above results, it was demonstrated that the 7-aminoquinolinone derivatives of the present invention inhibited the resistance to almost the same degree to the non-stimulation group as compared with a control group to which the test substance was not administered. Therefore, it is clear that the 7-aminoquinolinone derivatives of the present invention inhibit an increase in lung resistance induced by peroxynitrite exposure.

(Example 3)

This test was performed by estimating the antioxidative effect of the test substance using peroxynitrite quantitative method as a test system with dihydrorhodamine 123 so as to confirm the ability of the 7-aminoquinolinone derivatives of the present invention to scavenge peroxynitrite. This is a method described in NITRIC OXIDE: Biology and Chemistry Vol. 1, 145-157, 1997.

The test procedure will now be described.

(Preparation of the test substances and reagents)

1. Preparation of test substances

The test substance was weighted in an amount of approximately 10 mg, dissolved in a 10% Tween 80 solution and adjusted to 5×10^{-3} mol/L. Then, the solution was diluted

with 0.1 mol/L phosphate buffer (pH = 7.4) to 5 × 10^{-4} mol/L. The diluent was further diluted stepwise with a phosphate buffer containing 1% Tween 80 to obtain substance solution. The preparation was conducted before use. The final concentration of the test substance was adjusted to 3 × 10^{-6}, 1 × 10^{-6}, 3 × 10^{-7}, 1 × 10^{-7}, and 3 × 10^{-8} mol/L, respectively.

2. Preparation of peroxynitrite solution

1) Measurement of peroxynitrite concentration

To 20 μL of peroxynitrite solution (manufactured by DOJINDO LABORATORIES), 1980 μL of 0.1 mol/L sodium hydroxide was added and the mixture was diluted 100 times. The absorbance of the maximum absorption wavelength near 300 nm was measured using a UV-visible spectrophotometer and the concentration was calculated according to the following equation.

Concentration (mmol/L) = (absorbance/1670) × 100 × 1000

Based on the concentration calculated in the above section, dilution with a 0.1 mol/L sodium hydroxide solution was conducted and adjusted to 10 mmol/L. 990 μL of a 0.1 mol/L sodium hydroxide solution was taken into a 1.5 mL-Eppen tube. To the Eppen tube, 10 μL of a solution adjusted to 10 mmol/L was added to prepare a 100 μmol/L solution.

3. Preparation of dihydrorhodamine 123 solution

1) 25 mmol/L dihydrorhodamine 123 stock solution

Dihydrorhodamine 123 was dissolved into 1.155 mL of

dimethylsulfoxide, and adjusted to the concentration of 25 mmol/L. This solution was dispensed into 20 μL aliquots and then the aliquots were stored in a biomedical freezer (about −20°C) and used as a stock solution.

2) Preparation of 500 nmol/L dihydrorhodamine 123 solution

To 490 μL of 0.02% Tween 80 containing 0.1 mol/L phosphate buffer, 10 μL of 25 mmol/L of a thawed dihydrorhodamine 123 stock solution was added to make 500 μmol/L. The prepared solution was diluted with 0.1 mol/L phosphate buffer (pH = 7.4) 1000 times to prepare 500 nmol/L of a dihydrorhodamine 123 solution.

(Measurement of peroxynitrite scavenging activity)

1. Reaction operation

(1) To a 3.5 mL brown vial containing a stirring bar, 1470 μL of a 500 nmol/L dihydrorhodamine 123 solution and then 15 μL of the test substance solution was added. For the blank and control groups, 15 μL of 0.1 mol/L phosphate buffer containing 1% Tween 80 , as a solvent for the test substance solution, was added. After the addition, the mixture was stirred with a stirrer for 30 minutes.

15 μL of a 100 μmol/L peroxynitrite solution was added while stirring. For the blank group, 15 μL of a 0.1 mol/L sodium hydroxide solution was added. After stirring for 15 minutes, fluorescence intensity was measured.

2. Measurement of fluorescence intensity

Fluorescence intensity of the reaction solution was measured using a spectrophotofluorometer under the following measuring conditions: excitation wavelength, 500 nm; emission wavelength, 536 nm; measuring times, one; response, 1 sec; photomultiplier tube voltage, Low; band width at excitation side, 10 nm; bandwidth at emission side, 10 nm.

3. Calculation of oxidation rate of dihydrorhodamine 123

The oxidation rate of dihydrorhodamine 123 when adding the test substance was calculated, taking the oxidation rate of dihydrorhodamine 123 for control as 100, according to the following equation:

Oxidation rate (%) of dihydrorhodamine 123 = (measured value for each group - measured value for blank) / (measured for control - measured value for blank) × 100

Calculation of oxidation inhibition concentration (IC_{50})

50% oxidation concentration, that is 50% oxidation inhibition concentration (IC_{50}) was calculated by giving a straight line from two points surrounding 50% oxidation rate.

The results are shown in the following table.

Table 19

50% Inhibitory concentration on oxidation (IC_{50})

Compound	Concentration (μmol/L)	Compound	Concentration (μmol/L)
32	0.96	330	0.79
53	0.88	359	0.85
55	0.96	396	0.94
56	1.05	401	1.01
58	0.81	459	0.94
87	0.84	514	0.91
147	0.79	519	0.83
173	0.89	546	0.79
181	0.94	549	0.80
204	0.89	551	0.71
236	0.88	553	0.98
276	0.82	556	0.89
303	0.84	581	0.76
309	0.80		

From the above results, it was confirmed that all 7-aminoquinolinone derivatives of the present invention exhibited 50% inhibitory concentration of approximately 1 μmol/L or less, and inhibited the oxidative reaction by peroxynitrite.

(Example 4)

This test was performed so as to evaluate the pharmacological effect of the 7-aminoquinolinone derivatives of the present invention in an airway hyper-responsiveness model induced by inhalation of ozone in guinea pigs. The test procedure will now be described.

(Preparation of airway hyper-responsiveness model)

Guinea pigs were fasted for 18 hours or more. The animals were administered the test substance (30 mg/kg) and theophylline (100 mg/kg) one hour before ozone inhalation. For the non-stimulation group and the vehicle control group, vehicle (5 mL/kg) was administered similarly.

The animals were put into an acryl-made chamber (29 × 19 × 25 cm), subjected to induction of ozone generated by an ozonizer (EUV3-XU; EBARA JITSUGYO CO, LTD.) and exposed for 2 hours. The ozone concentration in the chamber was approximately 3 ppm. It was confirmed every 30 minutes that this concentration was maintained during exposure by an ozone monitor (EG-5000; EBARA JITSUGYO CO, LTD.) (measured value: 2.53 to 3.40 ppm). For the non-stimulation group, the animals were exposed to a mixed gas (oxygen: 95%, carbonic acid gas: 5%) similarly. The ozone concentration at that time was also confirmed similarly (acceptable concentration: 0.01 ppm or less, measured value: 0.00 to 0.01 ppm).

(Measurement of airway hyper-responsiveness for methacholine)

The measurement of airway hyper-responsiveness was performed 5 hours after the end of ozone exposure. The measurement of lung resistance (RLung) was performed according to the method of R. E. Giles et al. in the same manner as in Example 2. That is, the animals were anesthetized with Nembutal (Trade name: 50 mg/kg, i.p., sodium pentobarbital) and subjected to cannulation into

esophagus and trachea. The esophagus and trachea cannulas were connected to a respirator (ventilation volume: 6 mL/kg, ventilation frequency: 60 times/min, SN-480-7) and the RLung after inhalation of methacholine (100 μg/mL, for 1.5 minutes) was measured by the respiratory function analyzer (PULMOS-II; M.I.P.S) through a flow sensor (connected to Validyle DF45F (for flow rate) and DP45P (for pressure)). The inhalation of methacholine was performed with an ultrasonic nebuliser (NE-U17; Omron Matsuzaka) connected to the respirator under artificial respiration.

Used RLung represents 10 breaths having a stable value in a range from 1 to 30 breaths after initiation of each measurement for both before inhalation and during methacholine inhalation. The average of the RLung was calculated. The extreme values in RLung that occurred when animal moved during the measurement were excluded from the calculations.

The percentage of increase of RLung was calculated by the following equation.

Increase in lung resistance (%) = ([RLung after inhalation of methacholine]-[RLung before administration])/ [RLung before administration] × 100

Table 20

Increase in lung resistance (%)

Compound	Increase (%)	Compound	Increase (%)
32	32	359	31
53	29	396	22
55	26	401	25
56	30	459	26
58	27	514	31
87	29	519	26
147	29	546	27
173	30	549	28
181	25	551	22
204	37	553	28
236	28	556	25
276	30	581	30
303	27	Theophylline	26
309	34	Control group	60
330	22	Non-stimulation group	0

From the above results, it was confirmed that the 7-aminoquinolinone derivative of the present invention (dose: 30 mg/kg) showed, in spite of low dose, the effect which is almost equal to or greater than that of an existing drug, theophylline (dose: 100 mg/kg). Therefore, it is clear that the 7-aminoquinolinone derivatives of the present invention inhibit an increase in lung resistance induced by ozone inhalation.

(Example 5) (5% powders)

Compound of the present invention	50 mg
Lactose	950 mg

	1000 mg

Preparation example of powders of compounds 32 and 53 will be shown. The compound of the present invention was pulverized in a mortar and thoroughly mixed with lactose. The mixture was pulverized with a pestle to obtain 5% powders of compounds 32 and 53.

(Example 6) (10% powders)

Compound of the present invention	100 mg
Lactose	900 mg
	1000 mg

Preparation examples of powders of compounds 236 and 276 will be shown. In the same manner as in Example 5, 10% powders of compounds 236 and 276 were prepared.

(Example 7) (10% granules)

Compound of the present invention	300 mg
Lactose	2000 mg
Starch	670 mg
Gelatin	30 mg
	3000 mg

Preparation example of granules of compounds 303, 309, 330 and 359 will be shown. The compound of the present invention was mixed with the equivalent amount of starch and

pulverized in a mortar. The mixture was further mixed with lactose and the remaining portion of starch. Separately, 30 mg of gelatin was mixed with 1 ml of purified water, solubilized by heating, cooled and then mixed with 1 ml of ethanol while stirring to prepare a gelatin solution. Thereafter, the mixture prepared above was mixed with the gelatin solution and the resulting mixture was kneaded, granulated, dried and then sized to obtain granules of compounds 303, 309, 330 and 359.

(Example 8) (5 mg tablets)

Compound of the present invention	5 mg
Lactose	62 mg
Starch	30 mg
Talc	2 mg
Magnesium stearate	1 mg
	100 mg/tablet

Preparation example of tablets of compounds 514 and 519 will be shown. A 20 times larger portion of the above composition was used to prepare tablets each of which containing 5 mg of the active ingredient. That is, 100 mg of the compound of the present invention in a crystal form was pulverized in a mortar and mixed with lactose and starch. The thus prepared formulation was mixed with 10% starch paste,

and the mixture was kneaded and then subjected to granulation. After drying, the resulting granules were mixed with talc and magnesium stearate and then compressed in the usual manner. With the above procedure, tablets of compound 514 and 519 were prepared.

(Example 9) (10 mg capsules)

Compound of the present invention	300 mg
Lactose	2000 mg
Starch	670 mg
Gelatin	30 mg
	3000 mg

Preparation example of capsules of compounds 546, 549, 551 and 553 will be shown. Granules were prepared in the same manner as in Example 7 and packed in capsules in 100 mg portions. With the above procedure, capsules of compound 546, 549, 551 and 553 were prepared.

INDUSTRIAL APPLICABILITY

A drug comprising, as an active ingredient, at least one of a 7-aminoquinolinone derivative of the present invention and its physiologically acceptable salt has high safety and exhibits effectiveness against chronic obstructive pulmonary disease and therefore the drug can be utilized medically as a therapeutic agent for chronic obstructive

pulmonary disease.